Bart's syndrome associated with pyloric and choanal atresia

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Bart's syndrome, first described by Bart in 1966, consists of congenital localized absence of skin, congenital epidermolysis bullosa, and associated nail abnormalities. A newborn infant with Bart's syndrome is reported since it is a very rare condition, especially when associated with pyloric and concomitant choanal atresia. To the best of our knowledge, this is the first report presenting a case of Bart's syndrome associated with choanal atresia.

Key words: Bart's syndrome, congenital absence of skin, epidermolysis bullosa, pyloric atresia.

Bart's syndrome is clinically described as the association of congenital localized absence of skin (CLAS), epidermolysis bullosa (EB), and nail abnormalities[1]. CLAS is regarded now as a manifestation of EB. We report a newborn case of Bart's syndrome because it is an exceedingly rare disorder. This case had pyloric atresia (PA) and unilateral choanal atresia. To the best of our knowledge, choanal atresia is reported for the first time in a Bart's syndrome patient.

Case Report

A female newborn born by normal vaginal delivery at the 38th week of gestation revealed the absence of skin on lateral sites of her face and nose, neck, parietotemporal regions of the scalp, right leg above the ankle, and left leg above the knee, as well as the dorsa of both hands and feet. She was the third child of a non-consanguineous couple. The mother had a history of two intrauterine fetal losses due to intrauterine growth retardation and fetal abdominal cyst. She also used thyroid hormone replacement therapy until the last three months of her pregnancy. Polyhydramnios and gastric dilatation were detected in the antenatal ultrasound. The birth weight, length and head circumference were 1690 g (<3rd percentile), 41 cm (<3rd percentile), and 34 cm (50th percentile), respectively. In addition to the absence of skin, she had hypoplastic nails, and blistering on lower lip mucous membranes and on the anterior surface of the right knee (Figs. 1, 2). We could not pass the feeding tube from the left nostrils to the pharynx. On the plain abdominal X-ray performed in our neonatal intensive care unit, where the patient had oral secretions, we detected a single gas field bubble representing the distended stomach with no distal gas (Fig. 3). The patient was diagnosed as having congenital pyloric atresia and could pass only very little meconium. However, no intestinal gas inlet was observed on radiographs performed intermittently. We detected some blisters and peeling on the skin of the legs and left gluteal area after the first day, during the follow-ups (Figs. 4, 5). Complete blood count revealed leukocytosis. From the sixth day of hospitalization, a gradual increase in creatinine and blood urea nitrogen (BUN) levels was detected. Subepidermal blistering was seen on the skin biopsy, which could be associated with the group of congenital EB. Periodic acid- Schiff (PAS) stain was performed to examine the position of the basal lamina, and this was observed in the blister floor (Fig. 6). In the direct immunofluorescence examination with immunoglobulin (Ig)G, IgA, IgM, and C3, no deposits were observed. Echocardiography and cranial and abdominal ultrasound examinations were normal. The patient received supportive care including total parenteral nutrition with umbilical catheter, antibiotic therapy and aspiration of gastric

drainage through a peripheral central catheter, as well as sterile wound care. On the fifteenth day after her birth, the patient with poor general condition died due to suspected septicemia and acute renal failure.

Discussion

Bart's syndrome was first reported in 1966 in a family with CLAS on the lower leg, widespread blistering of the skin and mucous membranes and nails dystrophy[1]. EB-CLAS cases were reported in the literature[2,3]. The pathogenesis of aplasia cutis congenita (ACC), in the setting of EB, is unknown. Mechanical trauma could occur from fetal movements, such as rubbing, leading to *in utero* blistering with subsequent erosions[4]. Most commonly, the limbs and extremities and also sometimes the parietal and occipital region of the scalp are affected in CLAS[5]. Symmetric distribution, sharply demarcated borders, and involvement of toe webs and soles are frequent, so that physical trauma *in utero* was deemed too simplistic of an explanation for the defect[6]. The cases with PA associated with EB-CLAS were first described in 1982 by Carmi et al.[7]. The combination of EB-PA is considered in EB with an intense proliferation of connective tissue, partially or fully obliterating the pyloric lumen and sometimes the respiratory and urinary tracts as well[8,9]. Antenatal ultrasound may show polyhydramnios and gastric dilatation as manifestations of upper gastrointestinal obstruction[5]. Our case also had polyhydramnios history detected in the antenatal ultrasound, and the mother had two intrauterine fetal deaths with abdominal cysts. In addition to the extensive absence of skin and left choanal atresia at the postdelivery examination, we detected PA with abdominal radiologic examination. After the first day, some bullae and blisters were observed on the skin of the gluteal area and lower extremities and in the oral mucosa.

The explanation of the pathological process leading to the EB-PA-ACC phenotype was based on histopathological findings. The basic pathology involves at least two elements: the integrity of the basement membrane and hemidesmosomes and the control of the normal process of fibrosis occurring in the course of wound healing. The sequence of events is initiated by the separation of epidermis or the intestinal mucosal layer along with disintegration of hemidesmosomes. Then, an inflammatory response takes place, with massive fibrosis penetrating the deep layers and causing destruction of skin and obstruction of the intestinal lumina, especially in anatomically narrow passages[4]. This hypothesis is supported by new findings regarding the molecular basis of the EB-PA phenotype. Zelickson et al.[10] analyzed Bart's kindred and demonstrated poorly formed anchoring fibrils and cleavage below the lamina densa on ultrastructural analysis. Genetic linkage studies mapped the gene for the disease in this family to chromosome 3p at or near the site of the gene encoding type VII collagen (COL7A1). Christiano et al.[11] performed mutation analysis in this family by DNA sequencing, which resulted in glycine to arginine substitution within the triple helical domain of type VII collagen in the affected individuals.

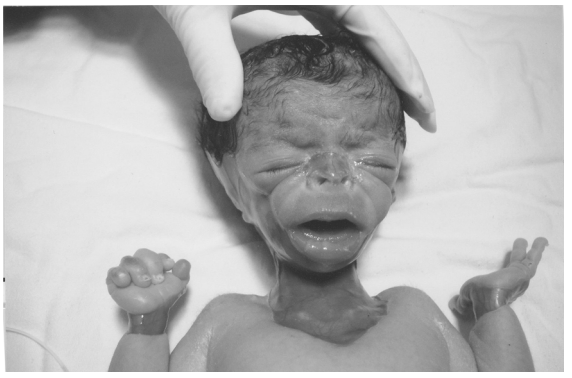

Fig. 1. Absence of skin on the face, neck, wrist, and dorsa of hands.

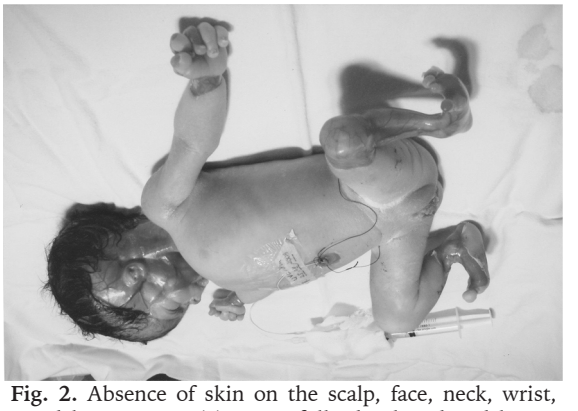

Fig. 2. Absence of skin on the scalp, face, neck, wrist, and lower extremities, not fully developed and low-settled ears, and erosion of phalanges.

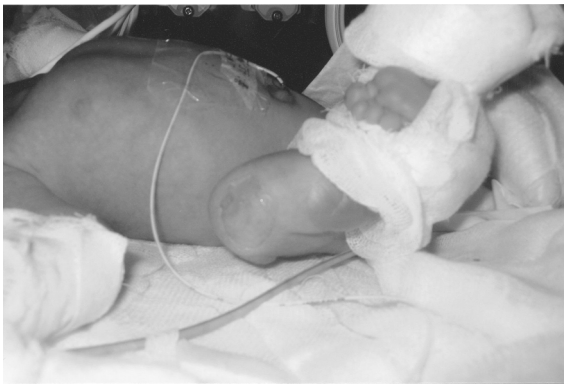

Fig. 3. Blister and erosion on the right leg.

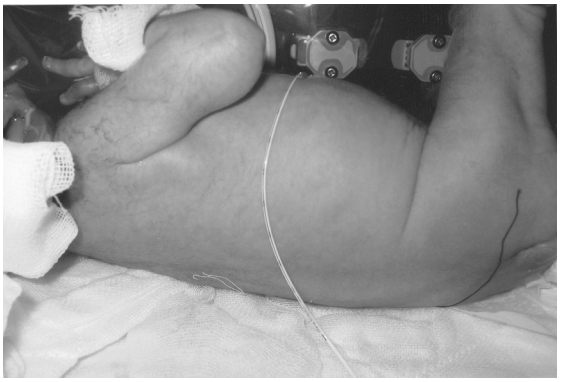

Fig. 4. Blister on the left gluteal area.

Epidermolysis bullosa (EB) is divided into three subtypes according the histopathologic location of the bullae: EB simplex (intraepidermal bullae in the suprabasal area), junctional EB (subepidermal bullae above PAS-staining basement membrane) and dystrophic EB (subepidermal bullae below PAS-staining basement membrane)[4,12]. Bart's syndrome may represent any of the three subtypes of EB. It is usually associated with dystrophic EB, and rarely associated with junctional EB and EB simplex[13,14] Originally described Bart's cases were shown to be dystrophic EB[10]. The Herlitz form of junctional EB is a rare variant of Bart's syndrome, usually lethal, that is produced by mutations in the genes coding for the anchor protein laminin 5[13].

The presence of PA is often seen in conjunction with junctional EB[12]. Involvement of the buttocks and paronychial inflammation are seen frequently in junctional EB[6]. In our case, PAS stain performed to determine the possible type of EB showed that positive staining basement membrane was in proximity to the blister base. This finding may suggest the possibility of EB simplex or junctional EB. Although a definitive diagnosis could only have been made using electron microscopy, which was not performed in our case, clinical features and histopathology favor junctional EB. Vidal et al.[15] reported on integrin β4 (ITGB4) mutation associated with junctional EB and PA. Birnbaum et al.[5] demonstrated that lethal EB-PA-ACC cases described by Carmi et al.[7] are the result of a large inframe deletion in exons 27-30 of the ITBG4 gene. Specific genetic defects of ITGB4 may interfere with the formation of hemidesmosomes to cause

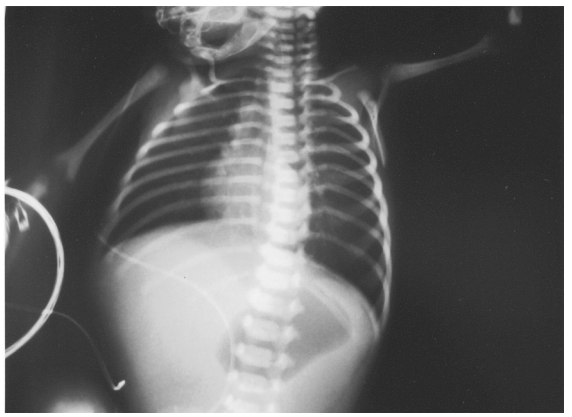

Fig. 5. Single large gastric air and absence of distal intestinal gas in direct abdominal X-ray.

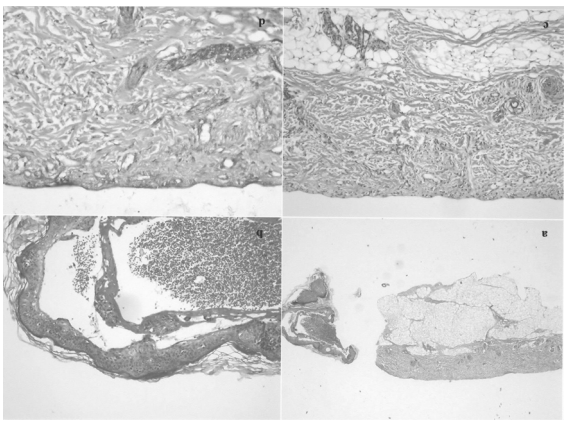

Fig. 6. a- Full-thickness epidermis and dermis seem to be completely dissociated (separated) in the panoramic view of biopsy (hematoxylin & eosin [HE] x40); b- Full-thickness epidermis forming the roof of the blister, and erythrocytes in cavity (HEx200); c- The base forming part of the papillary and reticular dermis. It is not possible to detect basal membrane with HE stain (HEX200); d- Basement membrane can be seen in the form of a thin violet line in the most superficial blister base with periodic acid-Schiff stain.

fragility of the basement membrane zone[4]. After obtaining family consent, our patient underwent ITGB4 mutation analysis due to the junctional EB-PA-ACC association, and deletion in the exon 27-intron 30 area was reported as negative. Studies for mutations in other possible candidate genes were not possible in our case.

Septicemia, electrolyte imbalance, protein loss, and failure to thrive complicate the severe exudative skin lesions, often leading to death in these cases. This has led to the recommendation that surgical treatment should be withheld in patients with PA-EB, and it is only suggested for neonates with PA-EB who are stable[12]. Our patient with poor general condition died with suspected sepsis and acute renal failure on the fifteenth day.

In newborns with congenital absence of the skin in the presence of bullae formation, Bart's syndrome should be considered, and the newborns should be examined in terms of developmental defects. Genetic counseling for affected families and sonographic follow-up in order to find evidence of upper intestinal obstruction in the prenatal period are extremely important for diagnosis of this rare familial disorder.

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